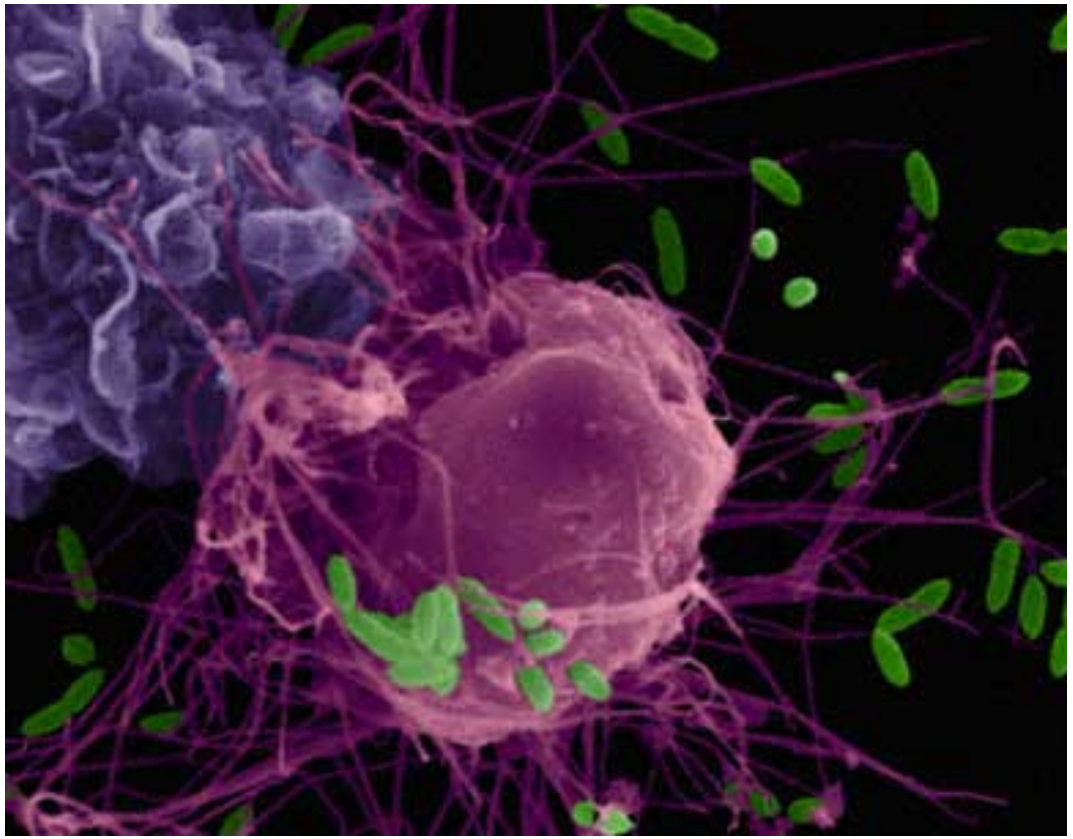
Modeling of Pathogen Host Interactions

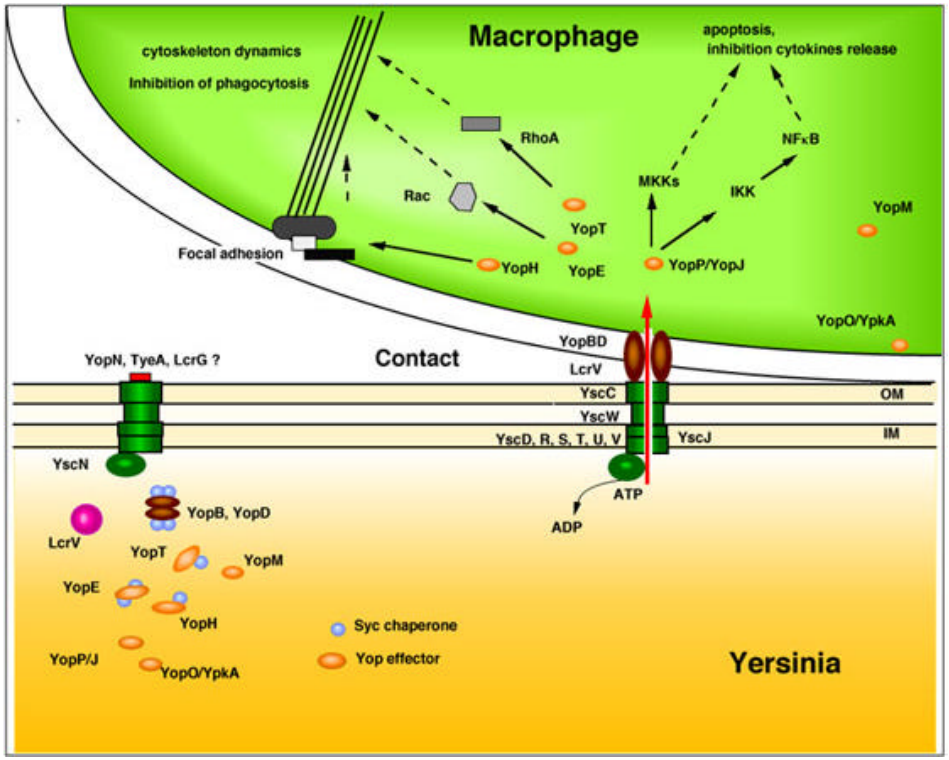
Carl Melius
And
Andrew Quong

Lawrence Livermore
National Laboratory

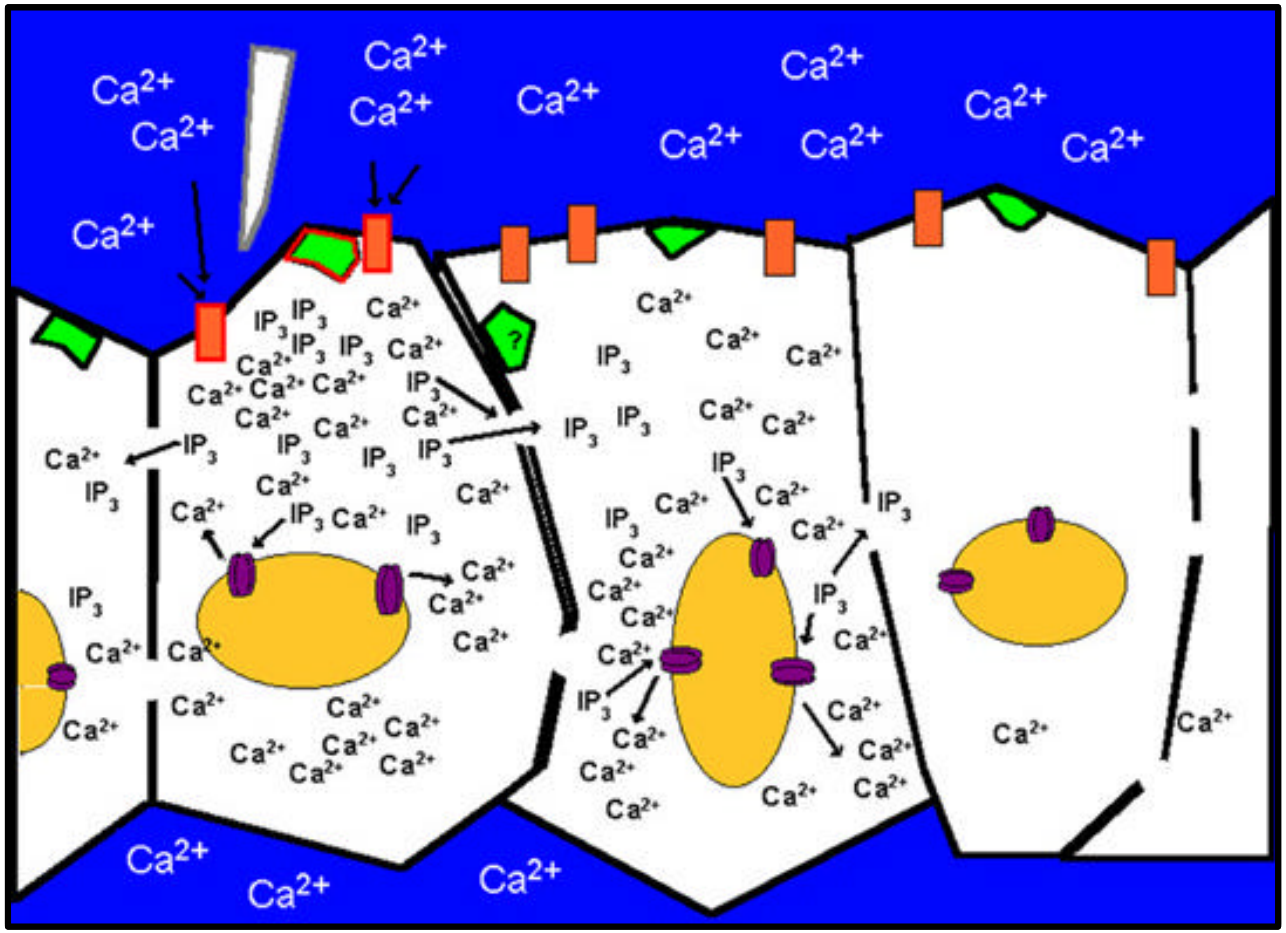


Yersinia pestis interactions with major cells of the human immune system

- *Yersina pestis* is responsible for the black plague epidemics
- Determine the gene regulatory network using DNA chips and proteomics



Mechanical stress causes calcium waves to propagate through epithelial cells



Cell behavior can be modeled with a set of reaction diffusion equations using ALE3D

$$\frac{\partial [Ca]}{\partial t} = D_{Ca}\nabla^2[\mathrm{Ca}] + \alpha\left(J_{channel} - J_{pump} + J_{leak}\right) + R_{buffering} \qquad \frac{\partial [IP_3]}{\partial t} = D_{IP_3}\nabla^2[IP_3] - k_{decay}\left([IP_3] - [IP_3]_0\right)$$

Cytosol

$$R_{buffering} = -k_{1,on}[Ca][B_1] + k_{1,off}[CaB_1] - k_{2,on}[Ca][B_2] + k_{2,off}[CaB_2]$$

$$\frac{\partial [B_1]}{\partial t} = -k_{1,on}[Ca][B_1] + k_{1,off}[CaB_1] \qquad \frac{\partial [B_2]}{\partial t} = D_{buffer}\nabla^2[B_2] - k_{2,on}[Ca][B_2] + k_{2,off}[CaB_2]$$

$$\frac{\partial [CaB_1]}{\partial t} = k_{1,on}[Ca][B_1] - k_{1,off}[CaB_1] \qquad \frac{\partial [CaB_2]}{\partial t} = D_{buffer}\nabla^2[CaB_2] + k_{2,on}[Ca][B_2] - k_{2,off}[CaB_2]$$

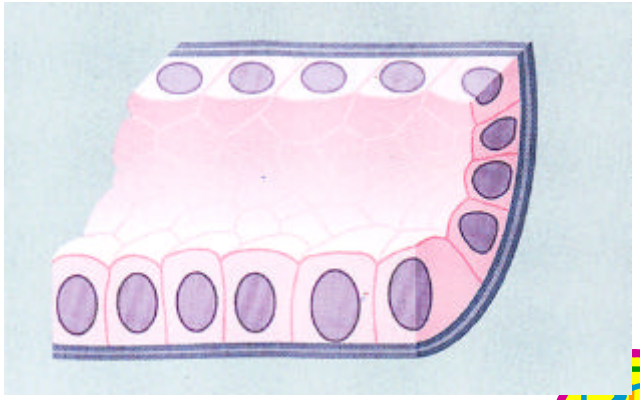
Li-Rinzel Ca/IP3 Dynamics

$$J_{channel} = J_{\max}\left(\left(\frac{[IP_3]}{[IP_3] + K_{IP_3}}\right)\left(\frac{[Ca]}{[Ca] + K_{act}}\right)h\right)^3\left(1 - \frac{[Ca]}{[Ca]_{ER}}\right),$$

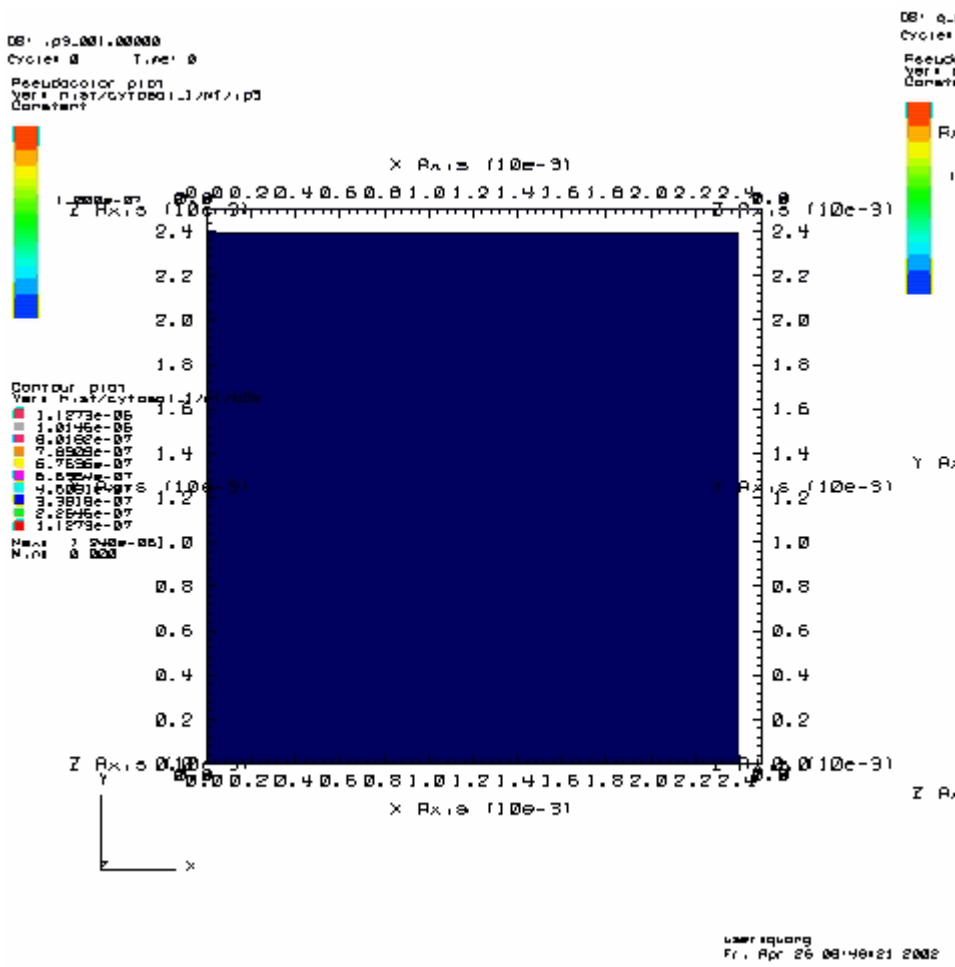
ER membrane

$$\frac{\partial h}{\partial t} = k_{on}\left(K_{inh} - \left([Ca] + K_{inh}\right)h\right),$$

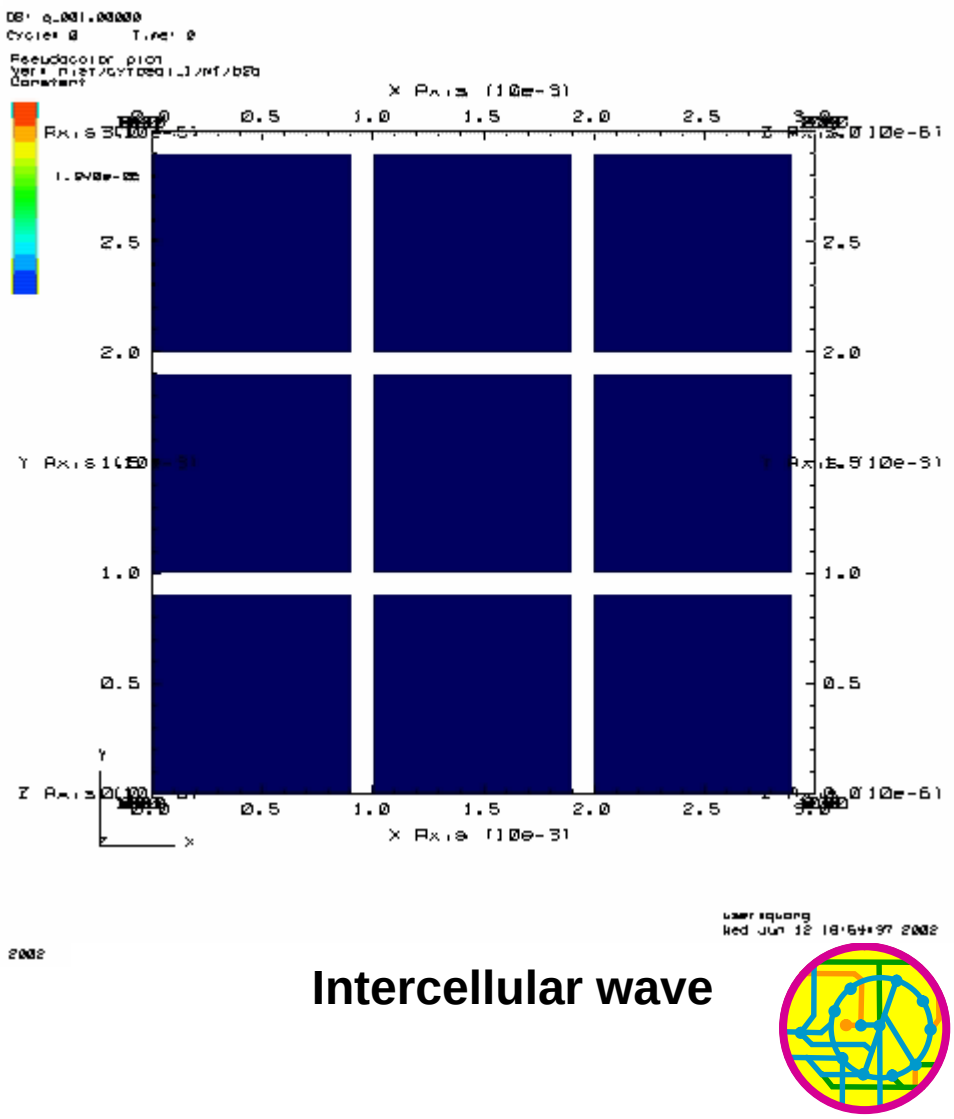
$$J_{pump} = V_{\max}\frac{[Ca]^2}{[Ca]^2 + K_p{}^2}, \qquad J_{leak} = L\left(1 - \frac{[Ca]}{[Ca]_{ER}}\right),$$



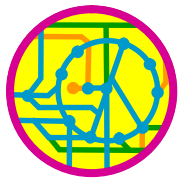
Model reproduces IP3 initiated calcium wave



Ip3 Initiated Wave

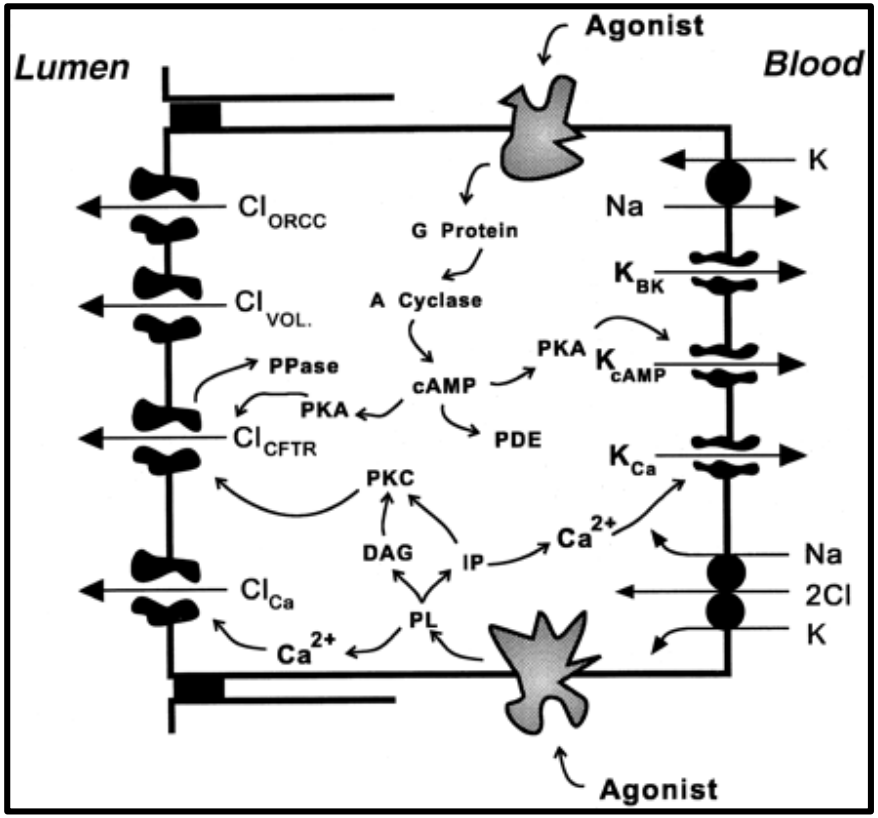


Intercellular wave

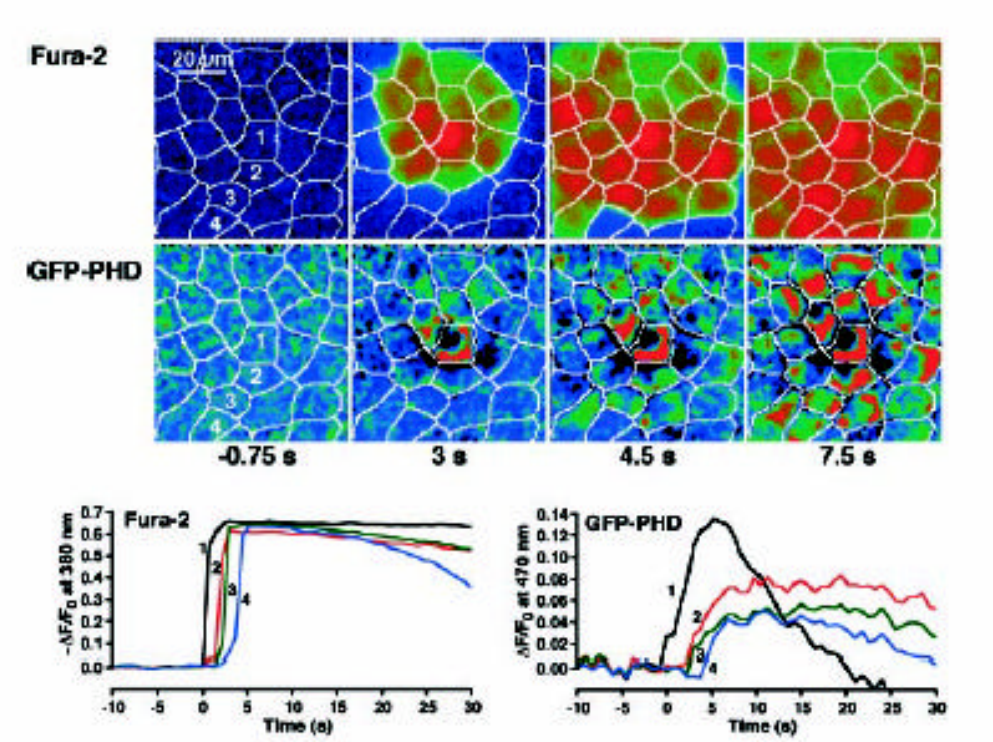


Ion transport across epithelial cells

- Use 3D adaptive Lagrange – Euler finite element code (ALE3D)
- Coupled PDE's describe transport
- Determine flux of Na^{+}, Cl^{-}, HCO_3^{-}, Ca^{++}, H_2O and compare with experimental data

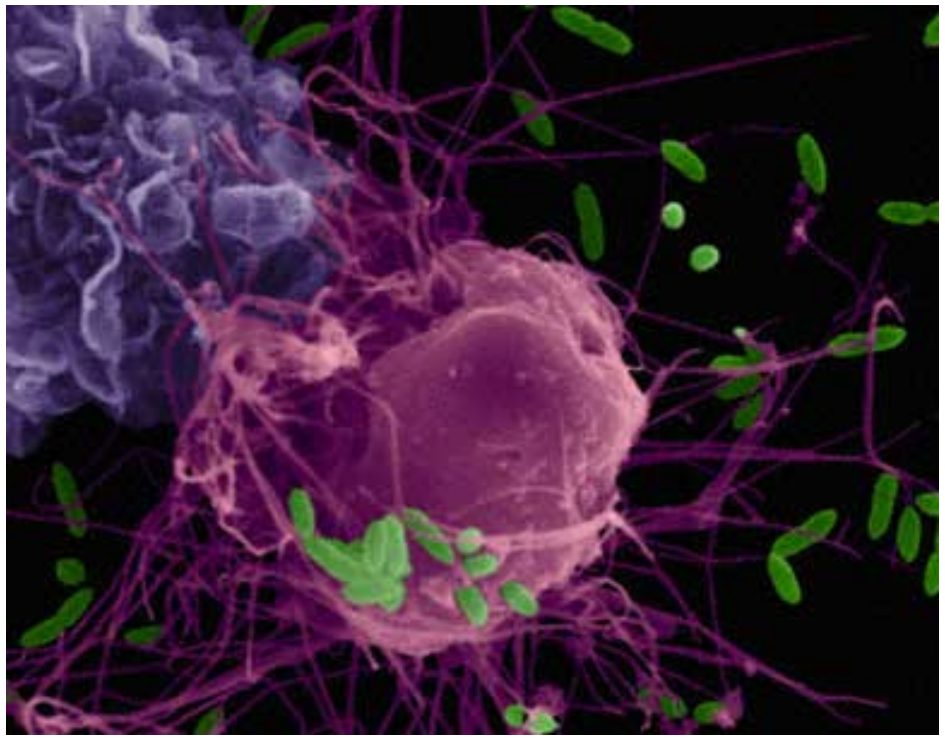


Experimental Measurements of Calcium and IP3 Dynamics With Confocal Microscopy

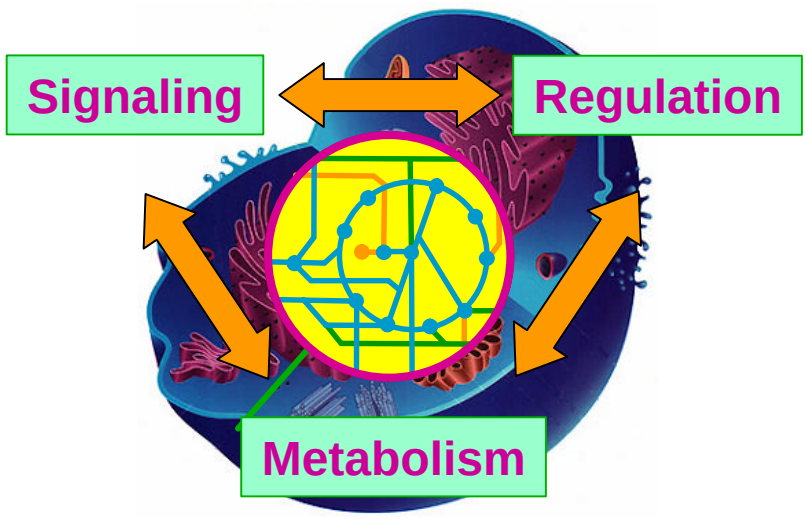


- Initiation of calcium wave within single cell
- Wave propagates through the tissue
- Fluctuations in Ca are seen
- Measured dynamics of IP3 and Ca

Hirose et al., Science, 284, 1527:1531, 1999.



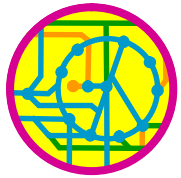
We are developing a multi-scale chemical reaction framework for biological systems



- Couple the metabolic, signaling, and regulatory pathways of biological systems
- Handle different time scales, concentration scales, and complexity scales
- Handle deterministic and stochastic integrators

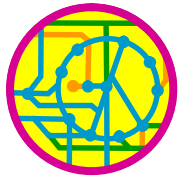
Epithelial cell calcium wave model will be extended

- Include other organelles such as the Golgi apparatus as well as the nuclear membrane
- Include stochastic model to treat
  - Isolated puffs (low excitability)
  - Abortive waves (medium excitability)
  - Steadily propagating waves (high excitability)
- Determine IP3 receptor density by
  - Immunohistochemisty and Western blotting
  - Isotopically labeled antibodies with nanoSIMS



Modeling of epithelial cells

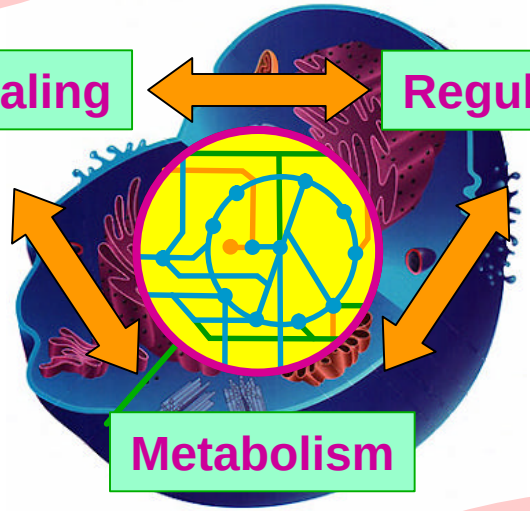
- Epithelial cells form the protective layer between the inside and outside of the body
- Involved in pathogen host interactions
- Provide both a 2-D and 1-D system for modeling
  - Intercellular Ca++ waves
  - Ion and water transport between inside and outside



Impact – Controlling cellular function will affect national health and security

Defeat genetically engineered organisms

Defend against new drug-resistant microbes



Defend plants / agriculture against pathogens

Shut off bacterial toxin production

Develop new drug delivery systems

Create new sources of food and energy

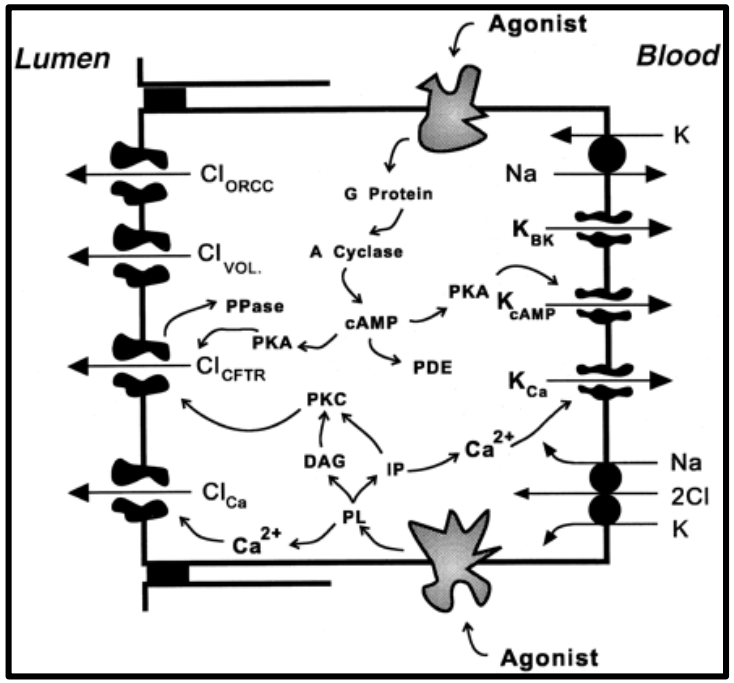
Epithelial cells are the body's interface to the world

Epithelial cells provide fluid secretion and salt absorption

Epithelial cells protect the body from the external world -- lungs, gut, kidneys

Genetic defects in the CFTR chloride channel causes cystic fibrosis

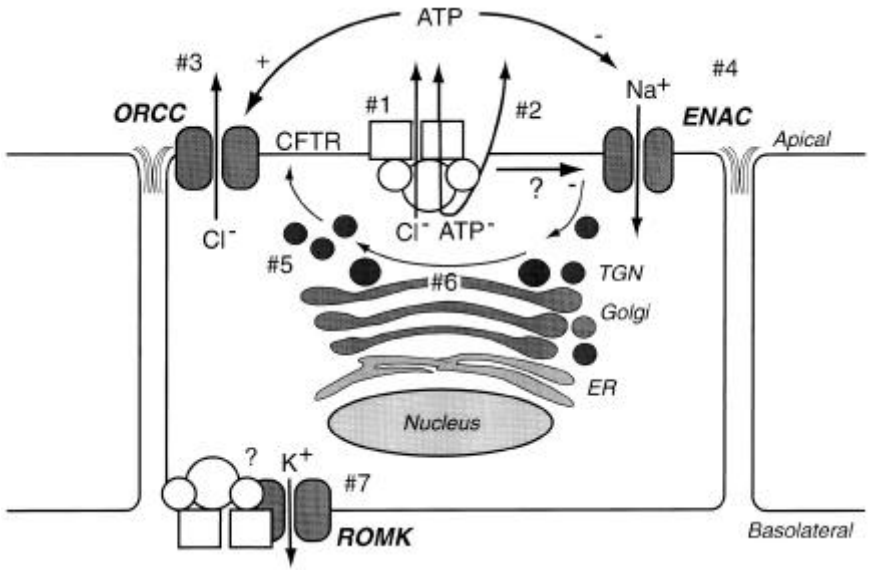
Pathogens induce secretory diarrhea



Epithelial cells regulate transport

Epithelial cells are polarized
- **Outside – Apical**
- **Inside – Basolateral**

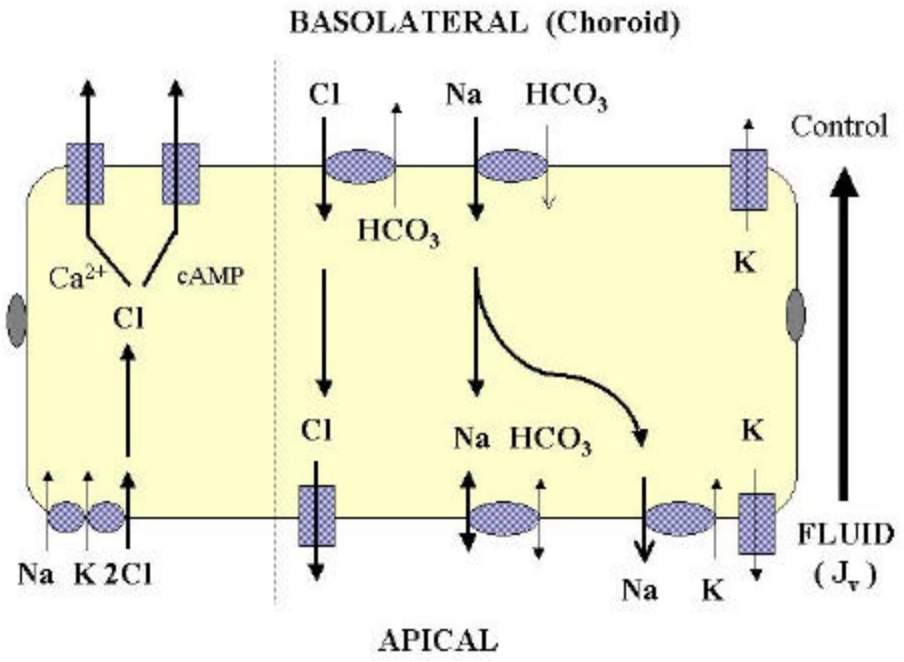
Apical and basolateral membranes contain different sets of ion channels, ion pumps, signal transducers



The 3-Dimensional Cell Model

- **Coupled PDEs describe transport**
- **Successfully applied to describe Ca++ movement**
  - **2D**
  - **Two components**

- **Implement model in ALE3D**
- **Include many components**

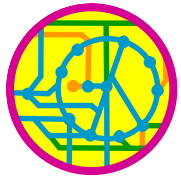


Parameters will be determined from published experimental data but need input from Quantum and Statistical mechanical methods

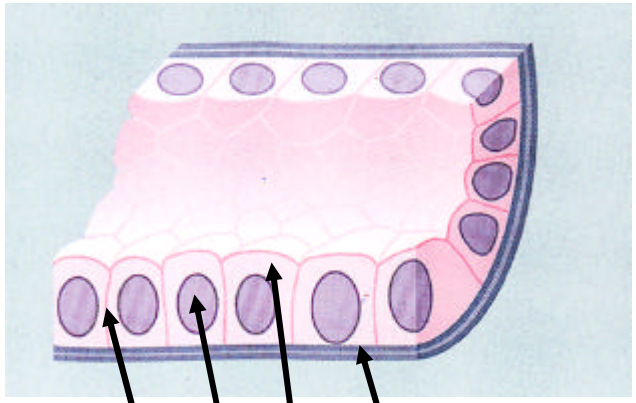
Why Study Epithelial Cells?

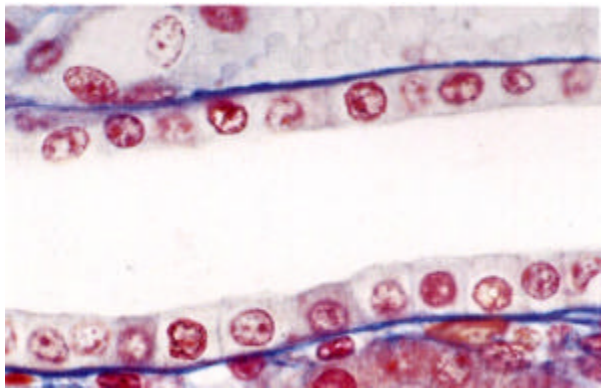
- **Epithelial cells line all cavities in the body.**
- **Form protective barriers that inhibit and control the movement of water, ions, etc.**
- **Understanding the interactions of Pathogens with people require an understanding of signaling pathways in epithelial cells**
- **Study normal cell function and pathogenic mechanisms of attack/disease**

Understanding the pathogen-host interactions requires an understanding of host cells



Cuboidal epithelial cells are more suitable for model development



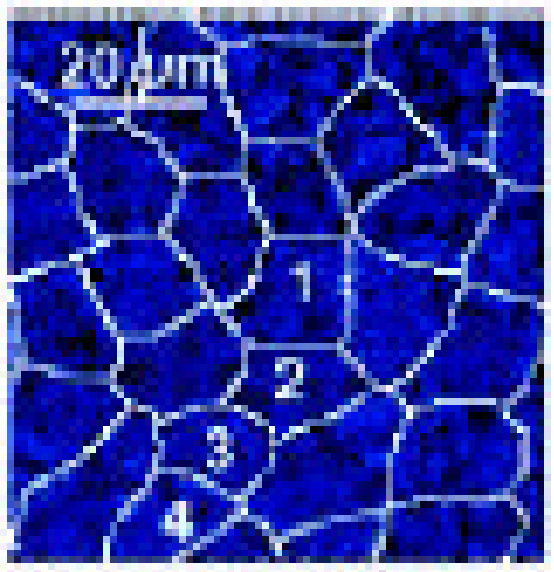


Cell membrane

Cytosol/ER/Organelles

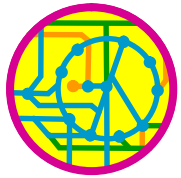
Nucleus

Gap Junctions



The two component model is nearly complete

- We will include additional structure and organelles in the cytosol, e.g. the Golgi apparatus
- Include a treatment of the nuclear membrane
- The IP3 receptor density will be obtained experimentally by
  - Established immunohistochemisty and Western blotting techniques with commercially available antibodies
  - Isotopically labeled antibodies and SIMS
  - SIMS work will be performed as part of the LDRD project 01-ER-112



Stochastic Model of Intracellular Calcium Dynamics Stochastic Model

Construction of a lattice model with the following ingredients:

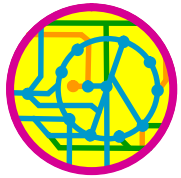
- **Each site represents a channel or cluster of channels**
- **Binding of IP_3 creates a percolating disordered network for potentially activated channels**
- **Activation of channels dependent on local calcium concentration**

Implement coupled lattice-gas/Potts model with a state variable s_n

$$S_n = \underbrace{r_n}\,\underbrace{S_n}$$

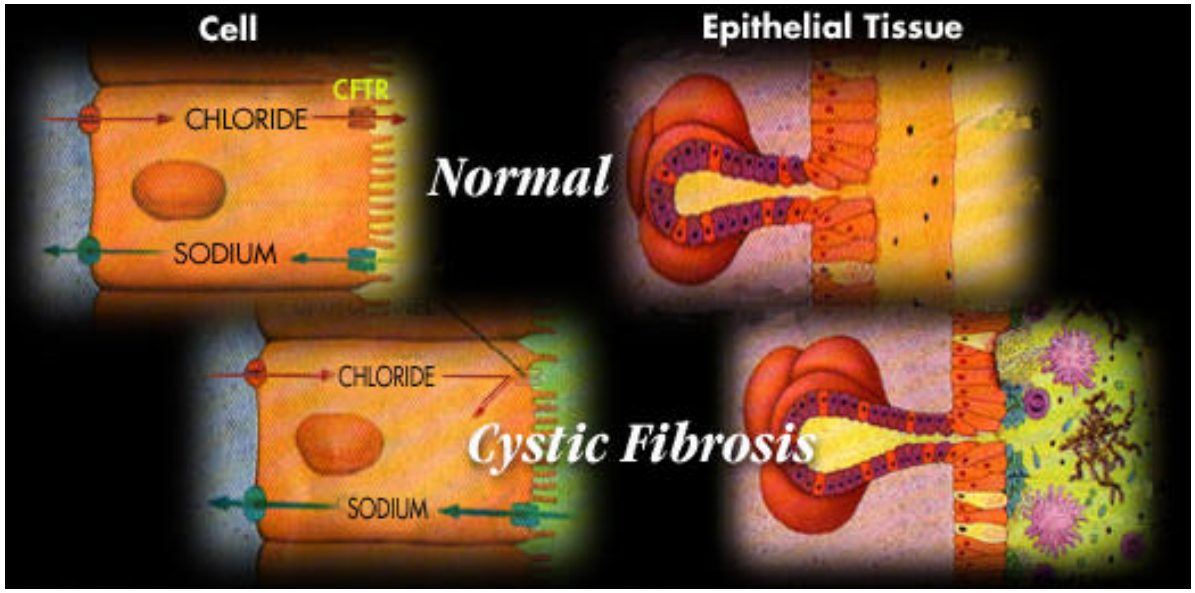
r_n = 0; no IP_3
r_n = 1; IP_3 bound

S_n = 1 activated channel
S_n = 0 deactivated channel
S_n = -1 inhibited channel



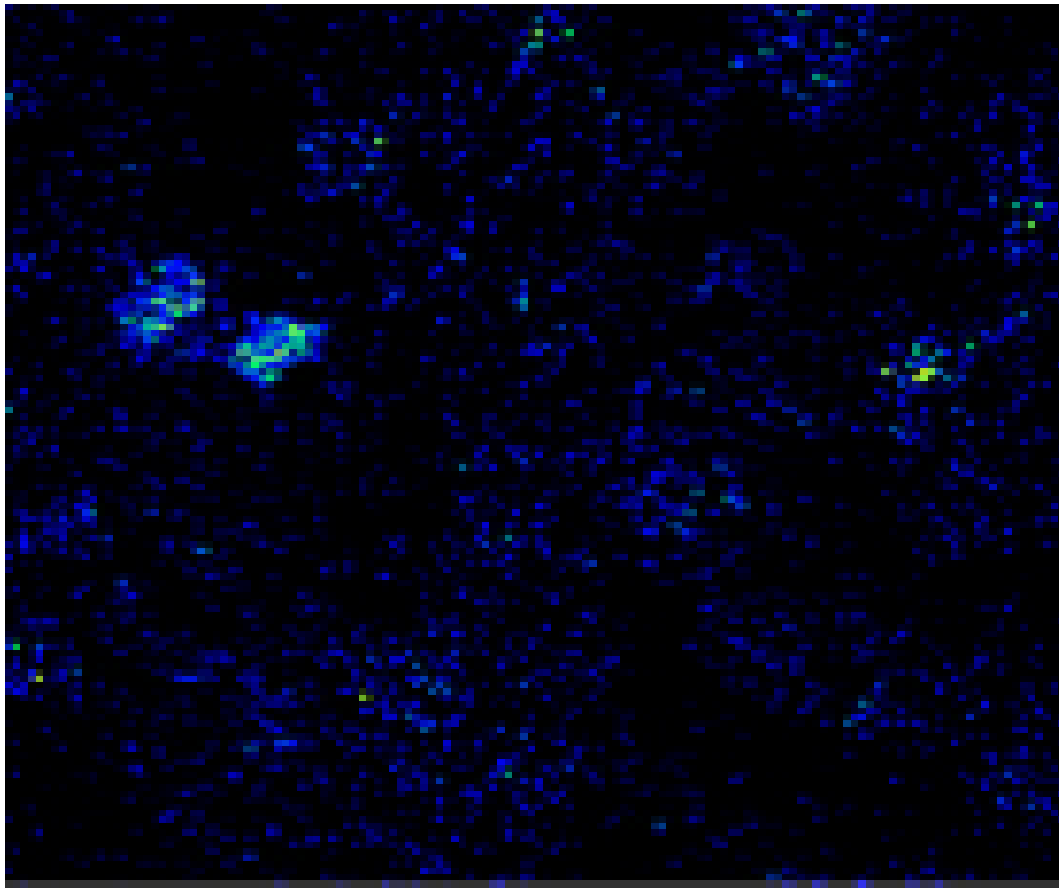
Model System: Ion Transport in Epithelia

- **Epithelia cells control the movement of ions, molecules, and water**
- **Cystic Fibrosis related to defect in Chloride transport (CFTR)**
- **The most common genetic defect amongst Caucasians**
- **Genetic origin of CF known, but not enough for a cure**



Ion transport of epithelial cells have been studied experimentally – data for model validation

Experimental Measurements of Calcium Waves With Confocal Microscopy



- Collection of cells
- Initiation of calcium wave within single cell
- Wave propagates through the tissue (IP3 mediated)
- Fluctuations in Ca are seen
- Need to couple this with IP3 Dynamics

http://www.neurobio.ucla.edu/webfacul/edirksen/monolye.gif

Statistical mechanical modeling of intracellular calcium dynamics

Calcium-induced calcium release is a autocatalytic process responsible for increase of intracellular calcium. This allows for complex spatiotemporal signals in the form of:

1. **Isolated puffs (low excitability)**
2. **Abortive waves (medium excitability)**
3. **Steadily propagating waves (high excitability)**

Can be seen with deterministic model, others have not

There exists evidence that the Ca^{2+} wave formation in cells is in a regime where stochastic effects are relevant.

Developing stochastic models in conjunction with deterministic models aids in elucidating the regimes where Ca^{2+} signaling is fluctuation driven

Stochastic models are needed to explain full range of wave phenomena